Baltimore declares O'Toole mistaken

Dr Margot O'Toole's comment on the OSI draft report reproduced in *Nature* two weeks ago, has drawn the following reply from Dr David Baltimore, one of the authors of an article alleged to include fraudulent data.

DOCTOR Margot O'Toole's recent comments on the draft report of the National Institutes of Health Office of Scientific Integrity (*Nature* **351**, 180; 16 May 1991) create a misleading impression and therefore require a response. The issues she raises have all previously been answered, often several times, but because many are not familiar with the details, I feel that it is necessary to demonstrate publicly that her charges lack substance.

I have already submitted comments on the draft report of the investigation conducted by the OSI into the controversy over the *Cell* paper. In them, I acknowledged certain errors of judgement on my part, commended Dr Margot O'Toole for her courage and insight and volunteered to participate in the continuing dialogue with Congress and other government bodies responsible for the oversight of scientific research supported by public funds.

The OSI report contained no allegations or findings that I participated in any falsification or fabrication of data, but its criticisms of me focused upon my defence of my co-author, Dr Thereza Imanishi-Kari, particularly at the May 1989 hearings before the congressional subcommittee. My comments explained that my defence of her grew out of the trust and respect I had for my collaborator's demonstrated abilities as a scientist, my understanding that the molecular analysis conducted in my laboratory validated Dr Imanishi-Kari's conclusions and my belief in the efficacy of the peer review process.

Since then, Dr O'Toole has commented publicly about my statement, and released a lengthy response to the OSI draft report that enumerates the charges she is now making. These are the remarks published in *Nature*.

Dr O'Toole's response, unlike the OSI draft report, contains allegations that I was aware before the completion of the OSI report that statements in the *Cell* paper were untruthful, that I was remiss in submitting a letter of correction to *Cell* citing the unpublished data by Dr Imanishi-Kari which Dr O'Toole states were false and that I have publicly attacked Dr O'Toole's competence and motives. For those reasons, I believe it is incumbent upon me to clarify these matters.

Dr O'Toole's response contains new charges that are different from her original constructive questions on matters of science, and also includes certain overstatements and errors. Any assessment of her claims must take into consideration a number of facts she has not mentioned, and I have therefore provided the information that follows.

■ **The importance of the notebooks discovered by Dr O'Toole.** Dr O'Toole begins her recitation of the history of the controversy by stating that in May 1986, she came across laboratory records "for experiments on which the central claim was based" and that it was "obvious" from those records that the experiment had not yielded the published results. She goes on to state that this flaw "remains evident", and that Herman Eisen of Massachusetts Institute of Technology (MIT) said to her that the evidence "appeared to indicate fraud".

The 17 pages of data Dr O'Toole copied were taken not from the notebooks of Dr Imanishi-Kari, but from those of Dr Imanishi-Kari's postdoctoral fellow, Moema Reis. Dr Reis's data have not been challenged. The major element of the 17 pages that appeared to contradict the study were data supposedly derived from a control mouse. These differed from the published data on control mice.

The article based on Dr Margot O'Toole's comment on the draft report by the NIH Office of Scientific Integrity (*Nature* 351, 180; 16 May 1991) has understandably provoked controversy. At issue is the authenticity of the data on which an article published in 1986 is based (Weaver, D. *et al. Cell*). This symposium of documents includes replies to O'Toole from two of those whom she criticized — Dr David Baltimore (president of the Rockefeller University) and Dr Herman N. Eisen (MIT) — as well as a much-abridged version of Dr Thereza Imanishi-Kari's comment on the OSI draft report, published in March (*Nature* 350, 263; 28 March 1991). Baltimore's own response to the same report appeared on 9 May (*Nature* 351, 94; 1991). Others who have signalled their wish to join this discussion will be accommodated as space permits.

It was discovered quite quickly, at the first meetings in May 1986 when Dr O'Toole raised her challenge, that the mouse in the 17 pages had been mistyped — it was not a control mouse and was in fact, transgenic. Data on truly normal mice were generated, and it was those findings that were used in the paper.

Although Dr O'Toole has acknowledged these facts in the past, she continues to charge that the 17 pages contradict the published paper, while neglecting to mention that the pages have proved to be irrelevant. By citing Dr Eisen's comment, she leaves the impression that the data she found are evidence of fraud. This issue has been definitively resolved and therefore, Dr O'Toole's statement that the discrepancy "remains evident" is incorrect, and her reference to the data she discovered and Dr Eisen's reaction to it is misleading.

■ **Dr O'Toole's challenge to Figure 1.** Dr O'Toole states that the paper's Figure 1 is "not truthful". She repeats at several points that experiments "central to the paper" had been performed, but did "not yield the published results". Dr O'Toole does not identify the experiments involved, but she has made such statements before when discussing the issues surrounding the reagent BET-1. Her original challenge focused largely on her belief that BET-1, a reagent used to distinguish between the antibodies that were the object of the study, and described in Figure 1, did not work. The airing of her views in 1986 led quickly to a realization that the specificity of BET-1 had been somewhat overstated in the paper.

Dr O'Toole repeats the allegations although this mistake was subject of a letter of correction to *Cell* in October 1988, two and a half years ago. This overstatement has been deemed a mistake by the Tufts, MIT and NIH reviewers and not the product of fraud.

Dr O'Toole persists in challenging Figure 1. Every academic committee or government agency that has reviewed the matter has rejected her contention that BET-1 does not work at all. Indeed, the January 1989 report of the first NIH panel pointed out that data showing the effectiveness of BET-1 could be found in Dr O'Toole's own notebooks.

■ **The subclone data submitted with the May 1989 letter of correction to *Cell*.** One of Dr O'Toole's most serious charges is that I published information as part of the 1989 letter of correction to *Cell* that I knew was false. Dr O'Toole states that the experiments on subcloning of the hybridoma wells in Table 2, described in the letter, were not in fact performed. Although she does not expressly state that I knew the data to be fabricated, her complaint that I submitted the letter to *Cell*, even after she told NIH in November 1988 that what have become known as the "June subcloning" experiments had not been performed, leaves the impression that I made a knowing misrepresentation. This conclusion is untrue.

First, I wish to state categorically that I have not throughout the history of this matter made a statement that was known to me to be untrue, or which I even suspected was untrue. In addition, I have never heard from Dr Imanishi-Kari that she did not perform any of the experiments described in the *Cell*

paper, or in the various published corrections. The fact that, in 1987, I called for a full review of the matter by NIH indicates that, in my mind, we had nothing to hide.

In November 1988, the first NIH panel to study the matter issued its draft report. Dr O'Toole responded and charged for the first time that the panel was drawing its conclusions from experiments which she said Dr Imanishi-Kari told her had not been done. She stated that Dr Imanishi-Kari told her during the course of the review by the Tufts *ad hoc* committee that no subcloning analysis of the Table 2 hybridomas had been performed and Dr O'Toole denied that subcloning data had been reviewed during those meetings. As I was not present during the Tufts meetings, and I had never heard Dr Imanishi-Kari make such a statement, I had no personal knowledge with which to verify or refute Dr O'Toole's remarks.

In December 1988, NIH solicited more information from Dr Imanishi-Kari and from Dr Henry Wortis, Dr Brigitte Huber of Tufts and Dr Robert Woodland of the University of Massachusetts, who had conducted the review for Tufts. All confirmed that in May 1986, they reviewed the data in support of Table 2, that the data supported Table 2 and its conclusions, and that the subcloning analysis was discussed with Dr Imanishi-Kari. The reviewers met with Dr Imanishi-Kari on 16 May 1986, when Dr O'Toole was not present.

The NIH panel stated in its final report that it carefully reviewed Dr O'Toole's letters, but found that no modification to its report was necessary. I believe, then, that my acceptance of the data as authentic at the time was justified. No forensic analysis had as yet been performed. Moreover, the OSI draft report states that Dr Reis told the investigators that she participated in performing the experiments.

■ **The isotyping experiments.** Dr O'Toole states that Dr Imanishi-Kari told me and the others assembled for the meeting with Herman Eisen of MIT in June 1986 that, in preparing Table 2 for publication, "she relied completely on her prior expectation of what the results would be", and she states that Dr Imanishi-Kari admitted in my presence "that a large series of the published experiments had not even been performed."

Dr O'Toole's failure to specify which experiments she means complicates any effort to respond, but the questions concerning the isotyping experiments on the Table 2 hybridomas were answered long ago. The experiments were in fact done, but — unknown to me at the time — the exact materials used were misidentified in the paper. The point was dealt with in the letter of correction to *Cell* in November 1988, and it is unclear to me why this issue would be raised now.

■ **The impact of the Secret Service briefing in 1989.** Dr O'Toole faults me for defending Dr Imanishi-Kari in my May 1989 testimony before Congress, even though the Secret Service and members of the staff of the congressional subcommittee had met me before the hearings to review the forensic findings. At that meeting, the Secret Service's work was still in progress; some of the irregularities the agents had uncovered in the notebooks were described to me in a very fragmentary and unsystematic fashion, without the aid of demonstrative charts or formal reports. The briefing did not touch on the evidence stressed in the recent OSI draft report — the analysis of paper used in the printer attached to the gamma counter.

The types of difficulties generally described to me — for instance, the obvious changing or adding of dates — seemed at the time to be as consistent with Dr Imanishi-Kari's known reorganization of her original materials as with any effort to commit fraud. When I met the Secret Service, I discussed at length how the notebooks had come to be put together.

For the reasons cited above, and because I had a high regard for Dr Imanishi-Kari, I did not abandon my faith in her at the time. In hindsight, as I have explained in my comments to OSI, it would have been prudent to step back and review the evidence before commenting further; my failure to do so demonstrates only my high degree of trust in a fellow scientist, and not any intent to deflect or obstruct an investigation.

Dr O'Toole expresses her view that I was not forthcoming with Congress because I did not explain that the pages of original data for the paper were organized into book form before being submitted to NIH in July 1988. I have made no secret of the fact that, when I first saw the records, they were not in books, but were a mixture of notebooks, loose paper and data sheets. Dr Imanishi-Kari acted on the advice of a lawyer and against my advice in pulling them together into an organized form to facilitate their review by scientists of NIH. I have stated this on numerous occasions over the years, as well as in interviews with OSI and the Secret Service.

■ **The 1991 retraction.** When summarizing the history of the matter, Dr O'Toole refers to the issuing of the OSI draft report and states: "Only then, five years after he learned of the problems, did Dr Baltimore retract the paper." This sweeping statement conveys the impression that "the problems" contained in the OSI report were known to me for five years, but the factual circumstances are quite different.

The serious allegations contained in the OSI report first became known to me in March this year, when the report was sent to me for comment. Five years ago, "the problems" identified by Dr O'Toole were of an entirely different nature. Her written memorandum to Dr Eisen of MIT in June 1986 specified the problems as she saw them. Then, Dr O'Toole expressed her view that the data did not support the paper's conclusion, and she proposed alternative explanations for the observed phenomena. In 1986, Dr O'Toole challenged the specificity of BET-1 and claimed that Table 2 understated the frequency of certain findings with respect to normal mice.

She challenged the paper's finding that it was the endogenous gene, and not the transgene, that was being expressed when idiotype-positive antibodies — that is, those characteristic of the transgene — were found in hybridomas from transgenic mice. Her argument was that the assays used were inadequate and insufficiently sensitive to detect the presence of the transgene. In other words, she questioned the accuracy of the paper's conclusion on matters of science.

In 1986 and 1987, Dr O'Toole was emphatic that she was alleging error, and not charging fraud. When she appeared before Congress in April 1988, she continued to stress that she was concerned only about error and basic scientific principles. Her allegations about the fabrication of the June subcloning data were not raised until late November 1988. Thus, her suggestion that I ignored charges of the seriousness of those contained in the OSI draft report for five years is not accurate.

Dr O'Toole also states that I "consistently and falsely" maintained that her objections were no more than alternative interpretations of valid data. The Tufts committee, Dr Eisen of MIT, and NIH reached precisely this conclusion and Dr O'Toole herself insisted in 1986, 1987 and 1988 that her only concern was for the validity of the science.

■ **Compliance with NIH recommendations.** Dr O'Toole states that the authors did not comply with the recommendation of the NIH panel contained in its January 1989 report. This statement is incorrect. We complied with all of the recommendations and the director of NIH accepted our response as appropriate.

■ **The meeting of Dr O'Toole, the authors and Dr Eisen of MIT.** Dr O'Toole provides a detailed description of the June 1986 meeting with Dr Eisen of MIT. Her account is couched in terms that incorrectly suggest that we were told then of a series of misrepresentations and that at the time I advised against a further public airing of her views.

First, Dr O'Toole states that I "acknowledged" at the time that the published results could not be based upon the data she brought to the meeting, that is, the 17 pages from Dr Reis's notebook described above. The 17 pages, as I have explained, had already been determined to be irrelevant.

Second, Dr O'Toole states that Dr Imanishi-Kari "admitted that a large series of the published experiments had not even been performed". It is simply not true that any large series of experiments had not been performed. Perhaps this overly broad reference is to the fact that the Table 2 idiotype type experiments were not done on the particular hybridomas indicated, but were performed on other hybridomas. That has already been the subject of a published correction.

If Dr Imanishi-Kari had stated at the meeting that she did not perform any of the

experiments, I would have immediately questioned the veracity of the paper. My remembrance that she made no such statement is supported by the sworn testimony of Dr Eisen before Congress that the question of tests not being performed never came up at the meeting.

Finally, Dr O'Toole states that I told her I would personally oppose any effort she might make to get the paper corrected. I do recall Dr O'Toole discussing, just as the meeting was ending, the prospect of her sending a letter to *Cell* specifying her criticisms. I did say, I believe, that the authors would then probably respond to her letter. I believe that such a response would have been appropriate in normal scientific disagreements.

Dr O'Toole's description of this exchange differs significantly from the account she submitted to Congress in April 1988 as part of her written chronology. There she states that I proposed that she could write to the journal and noted that I would respond. She goes on to say that she then "stated that [she] consider[ed] [her] responsibilities discharged and intended to drop the matter." Dr O'Toole's own previous version of the events contradicts the theory she is advancing now: that she wished to pursue the matter further in the journal, but that I intimidated her from doing so.

■ **My views on fraud in science**. Dr O'Toole purports to describe my views and incorrectly states that I maintain that "false claims do not have to be corrected because other investigators will stumble on error and clear things up eventually." This is a gross parody of my stated belief that the scientific process is the best means to test the scientific validity of published claims. As I have repeated in my articles on the subject, my congressional testimony and, most recently, in my response to the OSI draft report, consciously false claims, or fraud, by a scientist can never be excused or condoned.

■ **Dr O'Toole's claim that she has been personally attacked**. Dr O'Toole states that throughout the history of this matter, there have been "attacks on [her] competence and motives". She also states that she was subjected to "five years of slander and libel from Drs Baltimore, Eisen and Imanishi-Kari." Dr O'Toole makes this accusation, yet she cites not one example of any comment by me in which I publicly disparaged her or her ideas.

At the June 1986 meeting, I stated that I considered Dr O'Toole's criticisms to be imaginative and thoughtful. When Dr Eisen wrote a report about the meeting, he remarked, "I do not think that I or anyone present at the meeting felt that Margot O'Toole's disagreements were frivolous." None of my written statements or testimony about the matter raised any question about Dr O'Toole's abilities as a scientist or her motives. I told the congressional subcommittee that Dr O'Toole's criticisms "were a rational and appropriate part of the scientific process". My comments to OSI stated that her analyses were insightful, her expressions of concern were proper and appropriate and her motives were pure.

While Dr O'Toole has now directly attacked my honesty and integrity, none of my previous remarks nor any of the remarks in this statement were intended to criticize her personally, impugn her abilities as a scientist or question her motives. Rather, I have made this statement in the hope that any assessment of the validity of her comments will be a measured one, based upon a consideration of all of the facts and the entire record of this controversy, including Dr O'Toole's own previous statements on the matter.

David Baltimore

Origins of MIT inquiry

Dr Herman N Eisen, who conducted the inquiry at MIT in 1986, denies Dr O'Toole's account of its proceedings, and other charges.

Doctor Margot O'Toole makes a series of assertions that effectively charge me and many others with dishonest and irresponsible behaviour. These assertions cannot go unchallenged. In what follows, I address several of her more extreme statements, those that from personal knowledge I know to be inaccurate or grossly to misrepresent the true events.

It is important to clarify the circumstances surrounding the initial inquiry at MIT, now characterized by Dr O'Toole as a "cover-up". I met and spoke to Dr O'Toole on three occasions, all in the spring of 1986. First, she told me in March or April of experimental and personal difficulties she was experiencing in Dr Imanishi-Kari's laboratory. Second, on 30 or 31 May, she visited me at Woods Hole to describe her concerns about the validity of the Weaver *et al.* paper. Third, on 16 June 1986 she and I met the paper's authors (Baltimore, Imanishi-Kari and Weaver) to consider the memorandum she had prepared at my request.

In that memorandum (dated 6 June), Dr O'Toole elaborated clearly and at length on what she saw as four principal sources of error in the paper. However, it contains no suggestion that reported results were based on nonexistent or fraudulent data. I have read that memo many times since, searching for indications of the fraud that Dr O'Toole later proclaimed so vigorously but I have found none.

I have, therefore, long been puzzled by Dr O'Toole's turn-around in asserting — beginning, I think, two years later — that fraud was evident at the very start. Recently, however, I have come upon a hint of an explanation: in testimony before the Dingell subcommittee on 12 April 1988, Dr O'Toole stated that her memo of 6 June 1986 had been edited before being submitted to me to remove "any language that might possibly imply that she was alleging any misconduct".

She presumably took this action to avoid making an allegation of fraud without substantial evidence, as such a charge might expose her to legal action. While her trepidation is understandable, the result was a carefully manicured memorandum that contained no hint of fraud. In consequence, I was presented with a document that, except for its intensity and length, had all the hallmarks of a typical scientific dispute, the kind editors see repeatedly between authors and an intelligent, intensely engaged and critical reviewer of a manuscript.

Thus it is not inappropriate to ask: who misled whom? It is ironic and sad that, instead of recognizing that she bears some responsibility for creating a misleading situation, Dr O'Toole now characterizes the initial inquiry at MIT as a "cover-up". Given her choice of words, I also find it remarkable that those of us who were involved in the inquiry are accused of slander and libel.

I now consider the particular statements of Dr O'Toole's that are especially serious and that I find to be completely at odds with the events as I know them.

■ Dr O'Toole asserts that, at the 16 June 1986 meeting, "Dr Imanishi-Kari again admitted that a large series of the published experiments had not even been performed and that some which were performed had not yielded the claimed results." I deny that such a statement, amounting to a clear admission of fraud, was made at that meeting in my presence — and I was present throughout. Had such a striking confession been made at the time, it is difficult to understand why Dr O'Toole failed to mention it in her testimony before the Dingell subcommittee in 1988.

■ Dr O'Toole asserts repeatedly that the 17 pages she obtained from Dr Reis's notebook provided obvious evidence of problems with the paper. Her allegation grossly oversimplifies the complexity of the material. Walter Stewart, testifying two years later before the Dingell subcommittee, stated that the language in these pages was in "Portuguese or some other language" and that the pages were "extremely confusing because they consisted mainly of numbers". Earlier, I had asked him how long it has taken him to make sense of the 17 pages. He replied in one word: "weeks".

At the time, however, the presence in those pages of some data that did not agree with published material did not seem unusual. Notebooks commonly contain much imperfect data accumulated on the way to obtaining definitive results for publi-